REMARKS

Claims 19-25 and 29-32 are currently pending in the application. By this amendment, claims 1-18 and 34-35, which were previously withdrawn from consideration, have been cancelled; claims 26-28 and 33 have been cancelled; and claims 19-20 and 22-23 have been amended. The foregoing separate sheets marked as "Listing of Claims" shows all the claims in the application, with an indication of the current status of each.

Priority

Examiner has drawn Applicant's notice to the incorrect placement of the section entitled **CROSS-REFERENCE TO RELATED APPLICATIONS** which was inserted after the statement of funding in the original application. Applicant has hereby amended the specification by deleting the section from its incorrect location, and inserting the identical section at the appropriate location, immediately after the title of the application.

Applicant respectfully submits that this amendment to the specification adequately addresses Examiner's concern.

Drawings

Examiner has objected to the drawings of the application, stating that the photographs of Figures 1A-B, 3A-C and 4A-B are overexposed, and that no detail is discernible.

Applicant has hereby amended the drawings of the application and herewith submits replacement sheets of drawings for Figures 1A-B, 3A-C and 4A-B in which details of the photographs are more discernible. Applicant respectfully submits that this amendment to the drawings overcomes Examiner's objection.

Claim Objections

Examiner has objected to the recitation in claim 23 of "said expression cassette is Ad-EGFR-CD533" as incorrectly conveying the physical relationship between the expression cassette and Ad-EGFR-CD533, which is a recombinant adenovirus that comprises the expression cassette. Claim 23 depends from claim 22. Claims 22 and 23 have hereby been amended as follows: Claim 22 is amended to recite that the expressible nucleic acid molecule is in an

expression cassette "contained in a recombinant adenovirus", and claim 23 is amended to recite that the "recombinant adenovirus is Ad-EGFR-CD533". Applicant submits that these amendments result in a correct recitation of the relationship between the expression cassette, the adenovirus, and the term "Ad-EGFR-CD533". Applicant respectfully request withdrawal of this objection.

Claim Rejections under 35 USC § 112

Claims 19, 21, 22 and 24-32 stand rejected under 35 USC § 112, first paragraph, due to lack of enablement. Examiner states that this portion of the rejection would be overcome by limiting the claims to a carboxy-terminal deletion mutant EGFR that is dominant negative. Claim 19 has hereby been amended to recite that the expressible nucleic acid encodes a "dominant negative carboxy terminal deletion mutant epidermal growth factor receptor that is dominant negative". Claim 20, which depends on claim 19, has hereby been amended to accord with the amended language of claim 20. Applicant submits that this amendment to claim 19 overcomes this portion of the rejection.

In view of this amendment, Applicant respectfully requests withdrawal of this portion of the rejection.

Claims 19-27 and 29-32 stand rejected under 35 USC § 112, first paragraph, due to lack of enablement. Examiner states that the specification is, however, enabling for "radiosensitizing cancer cells generally *in vitro* or for radiosensitizing cancer cells *in vivo* specifically where the nucleic acid is administered directly to a tumor comprising cancer cells". Claim 19 has hereby been amended to recite that the cancer cells are *in vivo*, and that the nucleic acid is administered "directly to a tumor comprising cancer cells". Applicant submits that this amendment to claim 19 overcomes this portion of the rejection. Further, claims 26 -28 have been cancelled.

In view of this amendment, Applicant respectfully requests withdrawal of this portion of the rejection.

Claim Rejections under 35 USC § 102

Claims 19-22, 30, 32 and 33 stand rejected under 35 USC § 102(a) as anticipated by Reardon et al. (*Oncogene* 18(33): 4756-4766, August 19, 1999. Examiner states that the

declarations submitted with the previous response are sufficient to remove co-authors Reardon, Contessa, Mikkelsen, and Dent. However, the inventive entity of the publication is considered to be Schmidt-Ullrich, Valerie and Amir, absent evidence to the contrary.

Applicant herewith submits declarations signed by the co-inventors Schmidt-Ullrich and Valerie, in which they attest that they have reviewed the present application, including the claims, and the Reardon et al. publication, and that Amir is not an inventor of the claimed subject matter. Amir was a biostatistician under the supervision of Dr. Schmidt-Ullrich. His present whereabouts are unknown.

Applicant submits that this evidence is sufficient to establish that the inventive entity of the claimed subject matter is thus Schmidt-Ullrich and Valerie, and the publication by Reardon et al. is not a valid anticipatory reference against the present application.

In view of the foregoing, Applicant respectfully requests withdrawal of this portion of the rejection.

Claims 19-22, 32 and 33 stand rejected under 35 USC § 102(b) as anticipated by Zwick et al. *(J. Biol. Chem.* 272(40): 24767-24770, October 3, 1997). Claim 19 has hereby been amended to include the features of claim 28 (that administration to a patient is carried out *in situ* at the cancer locus) and claim 28 has hereby been cancelled. Claim 28 has not been deemed by Examiner to be anticipated by Zwick et al. Thus, the amendment of claim 19 to include the features of claim 28 renders claim 19 also not anticipated by Zwick et al. Applicant submits that this amendment overcomes this portion of the rejection.

In view of the foregoing, Applicant respectfully requests withdrawal of this portion of the rejection.

Claims 19-22, 30, 32 and 33 stand rejected under 35 USC § 102(b) as anticipated by Schmidt-Ullrich et al., (Proc. Amer. Assoc. Cancer Res. Abst. 533, March 1998). Claim 19 has hereby been amended to include the features of claim 28 (that administration to a patient is carried out *in situ* at the cancer locus) and claim 28 has hereby been cancelled. Claim 28 has not been deemed by Examiner to be anticipated by Schmidt-Ullrich et al. Thus, the amendment of

claim 19 to include the features of claim 28 renders claim 19 also not anticipated by Schmidt-Ullrich et al. Applicant submits that this amendment overcomes this portion of the rejection.

In view of the foregoing, Applicant respectfully requests withdrawal of this portion of the rejection.

Claims 19-22, 24, 32 and 33 stand rejected under 35 USC § 102(b) as anticipated by Wagner et al., (Int. J. Cancer 68(6):782-287, December 11, 1996). Claim 19 has hereby been amended to include the features of claim 28 (that administration to a patient is carried out *in situ* at the cancer locus) and claim 28 has hereby been cancelled. Claim 28 has not been deemed by Examiner to be anticipated by Wagner et al. Thus, the amendment of claim 19 to include the features of claim 28 renders claim 19 also not anticipated by Schmidt-Ullrich et al. Applicant submits that this amendment overcomes this portion of the rejection.

In view of the foregoing, Applicant respectfully requests withdrawal of this portion of the rejection.

Claim Rejections under 35 USC § 103

Claims 19-25 and 27-33 stand rejected under 35 USC § 103(a) as unpatentable over Greene et al. (US 6,417,168, hereafter "Greene") in view of Schmidt-Ullrich et al., Wagner et al., and Parker et al. (Proc. Amer. Assoc. Cancer Res. Abstr. 3581, April 1997). This rejection is traversed.

Claims 26-28 have hereby been cancelled, thereby making moot this portion of the rejection. The subject matter of claim 28 has been incorporated into claim 19.

The present invention provides a method for radiosensitizing cancer cells *in vivo* by delivering *in situ* to the cancer locus an effective dose of a nucleic acid that encodes a carboxy terminal deletion mutant epidermal growth factor receptor (EGFR, i.e., "ErbB1") that is dominant negative. Claim 19 of the application recites these features.

Example 3 of the application demonstrates the *in vivo* efficacy of the methods of the present invention to cause radiosensitization of human mammary carcinoma cells *in vivo*. Example 4 of the application demonstrates the *in vivo* efficacy of the methods of the present invention to radiosensitization of human malignant glioma cells. In addition, Applicant herewith

submits two recent publications co-authored by the present inventors in which further in vivo data is presented. Lammering et al. (*Radiotherapy and Oncology* 72:267-273, 2004) shows that the ability of the protein EGFRvIII to prolong survival of *in vivo* tumor cells exposed to radiation is completely abolished by the *in vivo* administration of EGFR-CD533 as described in the present invention. (See in particular, section 3.4). In Lammering et al., (*Clinical Cancer Research*, 10: 6732-6743, 2004), shows radiosensitization of tumors *in vivo* by the administration of EGFR-CD533 as described in the present invention. In particular, the results in this publication demonstrate that EGFR-CD533 inhibits a variant of ErbB1/EGFR called EGFRVII that is commonly over-expressed in brain tumors. EGFRVIII has a deletion (encompassing exon 2-7) in the extra-cellular domain resulting in a constitutively active kinase. CD533 is able to hetero-dimerize with EGFRVIII and inhibit its growth-promoting signaling and effects on tumors.

In contrast, Greene only generally discloses the use of tyrosine kinase deficient proteins that dimerize with members of the ErbB family of receptors (e.g. column 12, lines 46-49), and presents work done exclusively with ErbB2(p185) (as discussed below, EGFR/ErbB1 and ErbB2 are different), and provides no *in vivo* data whatsoever. Further, Greene teaches in column 18 at lines 53-56 that "According to some embodiments, variants of the p185neu/ErbB-2 receptor are used since this receptor has been shown to be the *preferred* partner for heterodimer assembly for all erbB family kinases..." (emphasis added).

An important major difference between ErbB2 and ErbB1/EGFR is that the former lacks an extra-cellular domain able to bind a growth factor (eg, EGF, TGF-alpha, etc.) and can therefore not be stimulated directly, whereas the latter contains an extra-cellular domain able to bind growth factors. Since the ligand binding domain is located within the extracellular N-terminal region of ErbB1/EGFR, this difference carries over into the C-terminal truncation mutants of these two species of ErbB proteins. In other words, C-terminal truncation mutants of ErbB1/EGFR (as employed in the present invention) contain active ligand binding sites whereas C-terminal truncation mutants of ErbB2 (as utilized by Greene) do not. This distinction was not discussed or alluded to by Greene. Selecting an ErbB C-terminal truncation mutant capable of ligand binding for use as a radiosensitization agent , as is done in the present application,

provides an agent that acts not only as a "decoy" for binding to and inactivating other members of the ErbB family, but also as a "decoy" for binding and retaining growth factors. The effects of administering such an agent are thus broader and more far-reaching than those of administering a C-terminal truncation mutant of ErbB2. All tumors produce increased levels of growth factors. In fact, a well-known phenomenon is autocrine growth, i.e., the tumor cell produces growth factors, some of which are tumor-specific, that in turn stimulate the tumors own growth. Thus, the ability to bind and scavenge growth factors in such tumors is an advantage pertaining only to ErbB1/EGFR C-terminal truncation mutants.

Another distinction between ErbB1/EGFR and ErbB2 (and their C-terminal truncation mutants) involves differences in the ability to form dimers. In general, both ErbB1/EGFR and ErbB2 proteins, when over-expressed (which is frequently the case in tumors) are able to hetero-dimerize with other ErbB family members. However, ErbB2 cannot homodimerize, i.e. ErbB2 can only hetero-dimerize with other members of the ErbB family. Therefore, ErbB2 and its mutated cancer-associated forms promote tumor progression in a ligand-independent fashion through hetero-dimerization with other ErbB receptors whereas ErbB1/EGFR does so in a ligand-dependent way through both homo- and hetero-dimerization. Furthermore, in addition to failing to homo-dimerize, ErbB2 does not form hetero-dimers or hetero-oligomers with TGF-alpha bound EGFR (Garrett 2003, copy enclosed). This is similar to the findings of Ferguson et al. (2000, copy enclosed), who showed that EGFR and ErbB2 did not form hetero-dimers in the presence of ligand. That study further showed that EGFR and ErbB4 (but not ErbB3) could form ligand-induced homo-oligomers, but only ErbB4 (efficiently) and ErbB3 (weakly) formed hetero-oligomers in the presence of ErbB2 and ligand. Thus, the performance of ErbB2 C-terminal truncation mutants with respect to forming inactive dimers is of a lesser scope and effectiveness than is that of ErbB1/EGFR C-terminal truncation mutants.

Clearly, Greene does not show or suggest radiosensitization of *in vivo* tumor cells by the *in situ* administration of a carboxy-terminal truncated EGFR. Greene provides no evidence that one of skill in the art would accept as conclusive that such administration would be effective. There would therefore be no motivation for one of skill in the art to combine the teachings of

Greene with teachings which utilize such constructs with an expectation of success. Greene therefore does not represent an adequate primary reference on which to build an obviousness rejection.

Examiner states that it would be obvious to combine Schmidt-Ullrich (*Proc. Amer. Assoc. Cancer Res.* Annu. Meeting 39:78, Abst. 533, March 1998) with Greene. However, Schmidt-Ullrich provides only limited *in vitro* data obtained in breast cancer cells. There is no discussion in Schmidt-Ullrich of *in vivo* administration of effective doses of a C-terminal truncated EGFR. Given the lack of predictability in the art, one of skill in the art would not assume based on Schmidt-Ullrich that *in vivo* administration of the construct to *in situ* tumor cells would be broadly efficacious, and a knowledge of Greene, as shown above, would not supply this deficiency. Applicant submits that much more than routine experimentation would be involved in order to arrive at the present invention based on a knowledge of Greene and Schmidt-Ullrich, and that the remaining two references do not make up for the deficiencies of the combination of Greene and Schmidt-Ullrich.

Examiner states that it would be obvious to combine Wagner et al. (hereafter "Wagner") and Parker et al. (hereafter "Parker") with Greene and Schmidt-Ullrich. However, Wagner teaches only increased sensitivity of cancer cells to cisplatinum in the presence of a truncated EGFR. Radiosensitization is not discussed. Similarly, Parker teaches only that expression of a dominant negative mutant EGFR can inhibit metastasis of colon cancer. Radiosensitization is not discussed. Neither Wagner or Parker discuss or allude to radiosensitization of *in vivo* tumor cells by the *in situ* administration of a carboxy-terminal truncated EGFR, as provided by the present invention.

In summary, there is no showing or suggestion in any of the references cited by the Examiner, and more particularly in the combination of those references, that would be accepted by one of skill in the art as demonstrating the feasibility of administering a carboxy-terminal truncated EGFR *in vivo* to cancer cells *in situ* in order to radiosensitize the cancer cells. This method was first described and proven to be successful by the present inventors. The claims of the present application directed to this method are therefore patentable.

In view of the foregoing, Applicant respectfully requests withdrawal of this rejection.

Conclusion

In view of the foregoing, it is requested that the application be reconsidered, that claims 19-25 and 29-32 be allowed, and that the application be passed to issue.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at 703-787-9400 (fax: 703-787-7557; email: ruth@wcc-ip.com) to discuss any other changes deemed necessary in a telephonic or personal interview.

If an extension of time is required for this response to be considered as being timely filed, a conditional petition is hereby made for such extension of time. Please charge any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,

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Amendments to the Drawings:

The three attached drawing sheets containing Figures 1A-B, 3A-C and 4A-B replaces the original drawing sheets for Figures 1A-B, 3A-C and 4A-B.